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ATTY.'S DOCKET: TORRES=1A

In re Application of:	)	Art Unit: 1648
Ramon TORRES	)	Examiner: S. FOLEY
Serial No.: 09/475,989	)	Washington, D.C.
Filed: December 30, 1999	)	
For: TREATMENT OF HIV-ASSOCIATED DYSMORPHIA/...	)	Confirmation No.: 7149

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
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Sir:

I, Ramon A. TORRES, hereby declare and state as follows:

I am the sole inventor in the above-identified application and my educational and professional experience was previously presented as Exhibit A in the Declaration Under 37 CFR §1.131 executed and filed on January 31, 2002.

Attached hereto as Exhibit A is my poster (number 675) and abstract, co-authored with K. W. Unger, J, Cadman and J. Kassous, entitled "The Effect of Recombinant Human Growth Hormone [rhGH] On Protease-Inhibitor-Associated Fat Maldistribution Syndrome [FMS]", presented at the 6th Conference on Retroviruses and Opportunistic Infections held in Chicago,

Illinois on January 31 - February 4, 1999. The poster was displayed at the conference and the abstract was published in the Program & Abstracts book.

The studies described in the attached poster were all conducted by me or under my direct supervision, and I can attest of my own personal knowledge that all the results reported in the attached poster and abstract are true and accurate.

The following discussion is directed to the distinction between obesity and HIV-associated dysmorphia dyslipidemia/dysmetabolic syndrome (HADDS).

Obesity is a chronic condition stemming from the interplay of a variety of environmental and genetic factors and is characterized by an excess of body fat, which is generally distributed evenly throughout the body. It is most often defined in terms of body weight adjusted for height as measured by the use of the body mass index (BMI), where weight in kg is divided by the square of the height in meters (Kg/m^2). Using this measure, the designation "overweight" is assigned to BMI between 25 and 30 and "obese" to BMI > 30. In obese individuals fat generally constitutes over 30% of body weight.

By contrast, HIV-associated dysmorphia dyslipidemia syndrome (HADDS) is a specific pathological condition attributable to the metabolic consequences of HIV disease and its treatment. HADDS (also known as HIV-associated adipose redistribution syndrome (HARS)) is a subset of the HIV

associated-lipodystrophy syndrome, first recognized and described in the late 1990's after the introduction of so-called highly active antiretroviral therapy (HAART) for the treatment of HIV disease. HIV associated-lipodystrophy syndrome covers a spectrum of morphological abnormalities and is characterized by regional accumulation of body fat, mostly in the trunk, in the dorso-cervical fat pad region ("buffalo hump") in the intra-abdominal cavity (visceral adiposity), and in the breasts (in women), often in association with regional fat loss (lipoatrophy) in other areas such as subcutaneous tissues of the face (with the loss of the fat pad of Bichat), limbs (with loss of fat in appendicular skeletal muscles), and buttocks. This abnormal distribution of fat results in dramatic negative changes in body habitus and facial appearance and causes severe psychological distress in many instances.

Lipodystrophy and HADDS occur in individuals of previously normal body morphology. Affected patients' overall height adjusted weight (expressed as BMI) is not in the obese range but the quantity of visceral fat is much higher than expected from an equivalent BMI in the healthy population (see attached Exhibit B, which is a graphical representation of data presented in the abstract of Kotler DP, Muurahainen N, Chang P, Engelson ES, Wang J, Heymsfeld SB. Anthropometric equations select HIV+ men and women with distinctly abnormal fat accumulation and distribution. XIV International AIDS

Conference, 2003), while the overall percentage of body fat is lower than that seen in obesity. Thus the distribution of fat in HADDS is markedly skewed, with less peripheral (limb and facial fat) than normal and more central (visceral and dorso-cervical) fat. The patients with HADDS and HIV-associated lipodystrophy may or may not be obese, may have normal, above normal or below normal BMIs depending on their height, weight and distribution of fat.

Compared to a healthy reference population, metabolic derangements, such as dyslipidemia and insulin resistance are common in HADDS and often severe. There is no evidence that these metabolic derangements were present in affected individuals before they developed HADDS and, indeed, some of the metabolic disturbances can be experimentally induced by the administration of certain anti-retroviral medications to healthy individuals.

Finally, in the treatment of HADDS with recombinant human growth hormone (r-hGH) large reductions in visceral fat, as determined by imaging techniques, were effected without loss of weight. This is in contradistinction to treatments for obesity which are often assessed entirely on the basis of body weight. Indeed, FDA guidelines for the pharmacological treatment of obesity specify body weight as an endpoint. The implication is that r-hGH therapy for HADDS, while effective in reducing visceral fat and dyslipidemia, would not meet these FDA

guidelines for the treatment of obesity.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

November 4, 2003
Date

Ramon A. TORRES

[illegible]

Exhibit A

6th Conference

on Retroviruses and Opportunistic Infections

Program & Abstracts

January 31–February 4, 1999

Sheraton Chicago Hotel and Towers,
Chicago, IL

Sponsored by the
Foundation for Retrovirology and Human Health

in scientific collaboration with the
National Institute of Allergy and Infectious Diseases
and the Centers for Disease Control and Prevention

Cosponsored with the
University of California, San Diego School of Medicine
Office of Continuing Medical Education

670 **Reversion of Lipodistrophy after Switching HIV-1 Protease Inhibitors to Nevirapine.** E. MARTINEZ*, L. LOZANO, I. CONGET, R. CASAMITJANA, and J. GATELL. Hosp. Clín., Barcelona, Spain.

OBJECTIVE: To assess the effect of switching from HIV-1 protease inhibitors to nevirapine on metabolic abnormalities of patients with lipodystrophy and on CD4/µL and viral load.

METHODS: 23 patients with <200 copies/mL, treated with 2 NRTIs and at least 1 PI decided to stop PIs because of changes in their body fat distribution. Nevirapine was offered to replace PIs. Physical examination, routine fasting cholesterol, triglycerides, glucose, and insulin, CD4 cells and plasma HIV-1 RNA were performed at baseline and every 3 months.

RESULTS: Twelve (52%) of the patients were males, age 40 years (27-60). Baseline CD4 cells were 514/µL (83-994). Awareness of fat redistribution occurred after a median of 12 months (6-26) from the onset of PIs. Eighteen patients had central obesity (16 also with peripheral lipodystrophy) and 5 patients had only peripheral lipodystrophy. Viral load had been suppressed a median of 9 months (3-14) prior to PIs withdrawal. Median follow-up from the replacement of PIs by nevirapine has been 7 months (range: 6-10). Six months after PIs withdrawal there was a significant improvement (p<0.05) in cholesterol (−21%), triglycerides (−56%), glucose (−16%), and fasting insulin resistance index (−46%) whereas CD4 cells remained unchanged (401/µL: range 57-941) (p>0.05); only one patient saw her viral load becoming detectable at a low count (546 copies/mL). Twenty-one patients (91%) reported a partial improvement in their fat distribution (particularly in peripheral fat wasting), although none of them admitted to be as prior to body changes.

CONCLUSIONS: Metabolic abnormalities including lypodistrophy associated with PIs may be at least partially reversible. HIV-1 suppression achieved with HAART including PIs may be preserved at least in the mid-term despite the replacement of a PI by nevirapine.

671 **[illegible] National Cholesterol Education Program (NCEP) Guidelines for the Identification and Treatment of Protease Inhibitor Related Lipid Abnormalities: Results of a Prospective Study**

K Henry[1,2], H [illegible][1], J [illegible][2], J [illegible][1], and J [illegible][1]. HIV Program[1] and Lipid Program[2], Regions Hospital and the University of Minnesota[3], St. Paul, MN, USA.

The use of protease inhibitors for the treatment of HIV-1 infection has been linked to rises in plasma lipid levels.

Objective: To utilize the NCEP guidelines to prospectively identify and manage increases in plasma cholesterol and triglycerides among persons with HIV-1 infection who are receiving protease inhibitors.

Methods: Review by a lipid specialist of 133 on PIs found that patients receiving ritonavir + saquinavir (60%; 35/53) were much more likely to have a significant increase (p < 0.001) in plasma lipids compared to patients receiving indinavir (32%; 20/62) or nelfinavir (39%; 7/18). 44 patients have been enrolled in a prospective study utilizing NCEP-based treatment. All patients had fasting lipid levels measured monthly and continued to receive PIs.

Results: 20 patients with mild increases in lipid levels (mean cholesterol = 245 mg/dl; mean TGs = 269 mg/dl) were initially managed with diet/exercise. At 6 months, the mean changes in lipids were: cholesterol = -17% and TGs = -21%. Drug intervention utilized gemfibrozil 600 mg BID (targeting TG elevations) and atorvastatin starting at 10 mg/day. For the 19 patients managed with both gemfibrozil and atorvastatin (baseline cholesterol = 314 mg/dl and TG = 1,359 mg/dl), by 6 months the mean changes in lipid levels were: cholesterol - 30% (p=0.004) and TG = -46% (p = 0.01). Due to concerns about drug interactions and risk for myopathy, patients were monitored for increases in plasma CK levels. None were observed.

Conclusions: Until more is known about the etiology and consequences of lipid abnormalities in HIV-1 infected persons, this preliminary data suggest that management of raised lipids associated with protease inhibitors can be carefully done following NCEP guidelines.

672 **Effects of Metformin on Insulin Resistance and Central Adiposity in Patients Receiving Effective Protease Inhibitor (PI) Therapy.**

T. SAINT-MARC*, J.L. TOURAINE. E. Herriot Hosp - 69437 LYON -FRANCE

Background: A syndrome of central adiposity (CA), hyperlipidemia, insulin resistance and coronary artery disease has been identified in patients receiving HIV-1 PIs. The purpose of our study was to determine wether metformin, a biguanide antidiabetic medication is able to change the clinical profile of the syndrome of CA in patients. Study design: Cross-sectional study. Patients: We recruited 21 PI experienced patients with CA (mean age 38.4 years, mean time of exposure to PI therapy 16.3 months, mean weight gain 3.1kg) known to have high fasting plasma insulin concentration (mean: 24.4mUI/l). Each patient participated in a 8-week protocol in one of the two groups: metformin (M) and control (C). At the beginning and the end of the study, we measured weight, height, waist-to-hip ratio, BMI, triglycerides, cholesterol, LDL and HDL cholesterol, apolipoprotein A1 and B, free fatty acid (FFA), testosterone, FSH, LH, SHBG, cortisol, albumin, CD4 and HIV viral load. Fasting plasma glucose and insulin levels were measured in the basal state and after a 75g oral glucose tolerance test (OGTT). Body composition was measured by BIA and visceral to total abdominal fat ratio (VAT:TAT) was assessed by abdominal CT. Results: The controls (12 patients) were similar to the group M with respect to age, BMI, CD4, VAT:TAT ratio and basal insulin levels. After the 8-week study period, the group M had a mean weight decrease of 2.1kg and waist-to-hip ratio decreased from 0.91 to 0.86, VAT:TAT ratio decreased from 0.81 to 0.72. There was a significant decline in the triglycerides, FFA, apo A1 and testosterone levels. Most impressively, mean basal plasma insulin levels decreased in groupe M while mean insulin levels increased in the controls (pre M: 23.6 ± 9.8mUI/l ; post M: 16.2 ± 5.4mUI/l vs pre C: 24.9 ± 10.2mUI/l : post C: 43.4 ± 14.6mUI/l). Data will be available for 30 patients. Conclusion: metformin appears to be effective for improvement in CA in PI-experienced patients.

673 **Effects of the PPAR-Activator Troglitazone on Protease Inhibitor Associated Peripheral Insulin Resistance.** K. K. WALLI*, G. M. MICHL, J. R. BOGNER, and F. D. GOEBEL. Ludwig-Maximilians-Univ., Munich, Germany.

Background: The induction of metabolic alterations (diabetes mellitus, dyslipidemia and lipodystrophy) is seen in patients treated with protease inhibitors (PI). We hypothesized that these side effects are due to peripheral insulin resistance. Therefore, the PPAR-activator troglitazone might be beneficial in the management of PI-associated metabolic complications.

Methods: In a pilot study, the effects of 400mg troglitazone od were investigated in 6 patients (age 41-57 years, BMI 24.2-27.4) with PI-associated diabetes mellitus. Markers of glucose homeostasis, serum lipids, CD4 count and viral load were followed for 3 months. Insulin sensitivity (i.v. insulin tolerance test) and lipodystrophy (bioimpendance and CT scan) were assessed at baseline and after three months.

Results: In all patients, fasting (decrease 15-50mg/dl) and postprandial glucose, fructosamide (decrease 15-46 mg/dl) and HbA1c (decrease 0.2-1.0%) levels improved after 8-12 weeks. After an initial rise, plasma lipid levels returned to baseline. No consistent pattern of dyslipidemia (i.e. changes in lipoprotein profile) was seen. Both CD4 count and viral load (67-514 cells/µL and lg 2.7 to lg 5.6 at baseline) were unchanged. Effects on insulin sensitivity and lipodystrophy were heterogeneous. Treatment was tolerated well in all patients, and no laboratory abnormalities (especially liver enzymes) were observed.

Conclusions: Troglitazone appears to be a well tolerated, safe and effective drug in the treatment of PI-associated metabolic complications.

674 **Incidence of Body Habitus Changes In a Cohort of 725 HIV-Infected Patients.** D. DIETERICH*, R. AYMAT, J. BRAUN M. MULLEN, A. MCMEEKING, K. WEISZ, S. KREISWIRTH, B. O'BRIEN, K. LAWSON, P. MERGENROEDER, and R. TIRELLI. New York Univ. Med. Ctr., St. Vincent's Med. Ctr., Cabrini Med. Ctr. and Liberty Med. LLP, New York, NY.

It has been suggested that hormonal therapy for the treatment of AIDS-related wasting may also reduce the incidence and severity of lipodystrophy-associated body habitus changes. Yet, limited data to justify this hypothesis are currently available. METHODS: As determined by visual inspection of facial atrophy, visceral fat increases, and peripheral fat decreases, we assessed the rates of body habitus changes among a population of HIV+ patients. RESULTS: 725 patients were included in this analysis. The median age of patients followed was 40 years; 91% were male and 72% were caucasian. The median baseline CD4+ count was 370 cells/mm3. At study entry, 34% had undetectable HIV-RNA. 80% were taking antiretroviral therapy at baseline, 96% of whom were receiving at least one protease inhibitor. A total of 437/725 (60.3%) patients were receiving some kind of hormonal therapy. Of these, 31 (7.1%) had physically apparent body habitus changes. Of the 243 (22.5%) receiving testosterone replacement therapy, 12 (4.9%) were experiencing body habitus changes. Of the 89 (12.3%) receiving nandrolone, 14 (15.7%) reported body habitus changes. Of the 4 patients receiving growth hormone, 1 (25%) experienced body habitus changes. Among the 101 patients receiving oxandrolone, body habitus changes occurred in 4 (4%). Elevated Cholesterol and Triglycerides were detected in only 12/31 (38.7%) patients with body habitus changes. CONCLUSION: Aggressive testosterone replacement and treatment of wasting with anabolics and growth hormone may lower the rates of lipodystrophy-associated body habitus changes, especially among patients receiving protease inhibitor-based therapy.

675 **The Effect of Recombinant Human Growth Hormone on Protease-Inhibitor-Associated Fat Maldistribution Syndrome.** R. TORRES** and K. UNGER*. *Bentley-Salick Med. Practice, New York, NY and *New York Univ., New York, NY.

Introduction: Fat maldistribution has been described in HIV+ patients on PI therapy who achieve maximal viral suppression, and is characterized by truncal adiposity [ta], peripheral lipodystrophy [pl] and buffalo hump [bh], associated with hypertriglyceridemia.

Methods: Eight HIV+ patients (2F, 6 M) maintained on PIs (6 indinavir, 2 ritonavir/saquinavir) for an average of 12 months who developed FMS were treated with rhGH (4-6 mg/day, sq), and evaluated prospectively with serial weights, blood lipid profiles, bioelectric impedance analyses and color photographs.

Results: All patients with FMS had elevated levels of plasma triglycerides +/− cholesterol. Four patients completed 3 months of rhGH and had notable improvements in fat maldistribution, with 25-75% reduction in bh and abdominal girth, but no change in pl. Weights were stable and there were no consistent changes in total body fat and blood lipids, despite 5-10% gain in fat-free mass. One patient discontinued rhGH due to carpal tunnel syndrome and had recurrence of FMS. Three patients have had > 6 months of therapy, one patient was lost to follow-up after 6 weeks of therapy and one patient has received < 8 weeks of therapy, yet at last observation all had a notable reductions in the size of and firmness of the bh and ta.

Conclusions: rhGH is effective in reducing buffalo hump and truncal adiposity, but not peripheral lipodystrophy and hyperlipidemia associated with PI therapy. Studies of rhGH in combination with other agents are needed.

Exhibit A

675

THE EFFECT OF RECOMBINANT HUMAN GROWTH HORMONE [rhGH] ON PROTEASE-INHIBITOR-ASSOCIATED FAT MALDISTRIBUTION SYNDROME [FMS]

Torres, RA*, Unger, KW†, Cadman, J*, Kassous JS, *Bentley-Satick Medical Practice, P.C., New York, NY, †New York University Medical Center, New York, NY, §Saint Vincents Hospital and Medical Center, New York, NY

INTRODUCTION

Changes in body habitus associated with metabolic derangements have recently been described in HIV-positive patients maintained on highly active antiretroviral therapy (HAART), specifically those including protease inhibitors. The disorders associated with fat maldistribution include the appearance of a dorsocervical fat pad (buffalo hump) and truncal and visceral adiposity despite facial and peripheral adipose tissue wasting (lipodystrophy). Increased breast size in women, nasolabial fold wrinkling, submandibular tissue swelling (chipmunk cheeks) and asymmetric bilateral or multiple lipomatosis, any or all associated with hypertriglyceridemia, hypercholesterolemia and/or insulin resistance. Cutaneous associated conditions include dry skin, acrodermal dysplasia, thinning hair and prominent leg veins. Patients are able to suppress dexamethasone and have normal levels of basal cortisol. Not all patients manifest all the characteristics of the syndrome and many have incomplete presentations,often with only one metabolic abnormality. It is unclear whether the syndrome represents an actual toxicity related to any elements of HAART, or a metabolic derangement associated with viral suppression, as most patients have evidence of inhibition of viral replication and viral loads below the level of quantification. Although the actual prevalence of this syndrome as well as its associated morbidity and mortality are not known, the disfiguring aspects of the changes in body habitus significantly impair quality of life, reduce patient empowerment and motivation to adhere with the antiretroviral regimen and may deter naive patients from starting therapy. In addition, the metabolic derangements have the potential for serious sequelae, such as severe hypertycerma, frank diabetes mellitus, premature coronary or cerebrovascular disease, gall stones, gout, osteoporosis and avascular necrosis of the hips. Strategies to manage the syndrome have been limited to alteration of the HAART regimen (drug discontinuation , dose reduction or switching drug therapies), cosmetic surgery (liposuction, excision of lipomas, face reconstruction) and treatment of the individual metabolic derangements with dietary interventions, exercise, lipid-lowering agents, oral hypoglycemics or insulin, among others. Due to the lack of understanding of the pathogenesis of the syndrome, a treatment aimed at reversing the condition has not been possible.

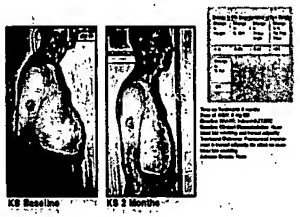
Recombinant human growth hormone (Serostim™) is effective in increasing body cell mass and fat-free mass through promotion of protein anabolism and lipid catabolism, in patients with HIV-associated wasting syndrome, and is FDA-approved for this purpose. A female patient (MC) maintained on an indinavir-containing regimen developed truncal obesity, a buffalo hump, chipmunk cheeks and hypertriglyceridemia, in addition to peripheral muscle wasting and lipodystrophy with associated fatigue and malaise. Treatment with Serostim™ (5 mg/kg) was effective in not only reversing the wasting process but also the altered body habitus, with rapid clearance of the hump and truncal obesity. This observation prompted the investigational open use of Serostim™ for HIV-infected patients with evidence of peripheral lipodystrophy, truncal adiposity or buffalo humps, as there are no effective treatments for these conditions, short of surgical liposuction. This report describes the experience to date of 13 patients followed by two HIV specialists, over a time period of up to 18 months.

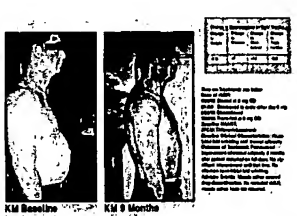
METHODS

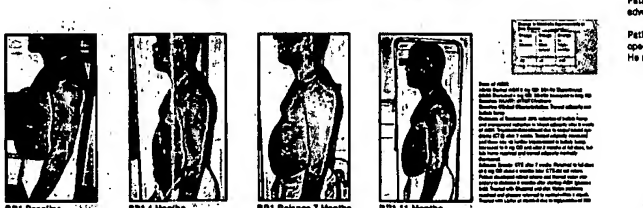
Thirteen AIDS patients on protease inhibitor-containing regimens (10 males and 3 females) presented with classic signs and symptoms of fat maldistribution to the HIV specialists; these included: Buffalo hump 8 (46%), truncal obesity 12 (92%), peripheral lipodystrophy 4 (30%), facial nasolabial fold thinning and wrinkling 4 (30%), breast enlargement 2 (15%). Metabolic abnormalities included hypertriglyceridemia in 6 (46%), hypercholesterolemia 5 (38%) and hyperglycemia 4 (30%). Patients were evaluated for Cushing's syndrome, diabetes mellitus and hypertension and then started on self-administered subcutaneous doses of Serostim (6 mg/day in males, 5 mg/day in females). Patients had baseline weights, physical examinations, lipid levels, hepatic and renal function tests, complete blood counts, urinalyses, bioelectric impedance analyses (BIAs) performed and photographs taken. At monthly intervals the laboratory, BIA measurements and photos were repeated and compared to baseline values. Assessments of treatment outcomes were mostly subjective due to the difficulty in computing photographs, lack of reliable surrogate markers and lack of access to MRI scanning. Changes in body habitus that could be measured due to comparable photographs were quantified using the width of the abdomen, but this did not capture the change in volume and shape of the body. Weights, laboratory values and BIA measurements were compared to the baseline values; drug was only discontinued for known toxicities and serious adverse events, and was reintroduced after adverse event resolved. Patients received treatment for any metabolic derangement as per their primary care physicians, according to established criteria; their antiretroviral regimens were also changed according to state-of-the-art guidelines issued by the NIH/PHS. Patients and their insurance policies were responsible for the payment of the drug, and were assisted by the Serostim Patient Assistance Program, if eligible.

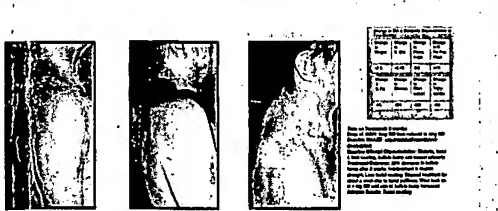
Mean Baseline Patient Clinical Characteristics

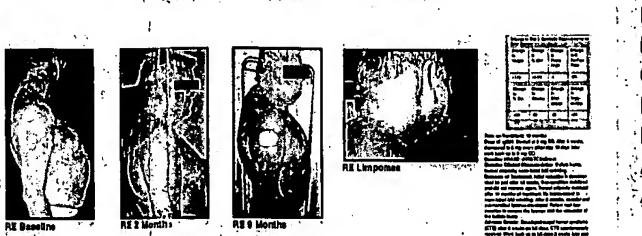
N	Age (Years)	CD4 Cell Count	Viral Load (copies/ml)	Cholesterol (mg/dl)	Triglycerides (mg/dl)	Glucose (mg/dl)	% IBW	Phase Angle	% Fat Free Mass	% Fat
13	43 (range 27-61)	383 (range 12-678)	31,872 (range <50-272,806	187 (range 127-301)	321 (range 104-674)	122 (range 83-397)	118% (range 91.5-130)	6.5 (range 5.4-8.2)	79% (range 66-91)	21% (range 9-34)











Bentley Health Care, Inc.

Outcomes of Treatment with rhGH in Patients Not Shown in Photos:

Patient MC: 50 year old Hispanic female developed truncal adiposity, peripheral lipodystrophy,enlarged breasts and buffalo hump while on indinavir containing regimen, associated with elevated cholesterol and triglycerides levels. Treated with rhGH (6 mg/day), she had total resolution of hump, 14 lb. weight loss associated with redistribution of truncal adiposity. Increased exercise tolerance but no significant change in lipodystrophy, serum triglycerides or cholesterol, and no adverse effects except for mild arthralgias. She remains on rhGH 18 months later.

Patient JD: 36 year old white male developed large buffalo hump, which impaired keeping head erect and buttoning shirt collar; after 2 months of treatment he had 50% reduction in size and firmness of dorsocervical fat pad. Adverse effects included elevation of pancreatic enzymes and serum glucose.

Patient RB2: 47 year old white male developed buffalo hump and truncal adiposity, after 1 month of treatment, he had minimal change in either abnormality, but no adverse effects. He remains on rhGH therapy.

Patient RT: 53 year old male developed truncal adiposity, after 1 month of treatment he had slight improvement in truncal adiposity without associated side effects. Developed lymphoma after 1 month and had to discontinued rhGH.

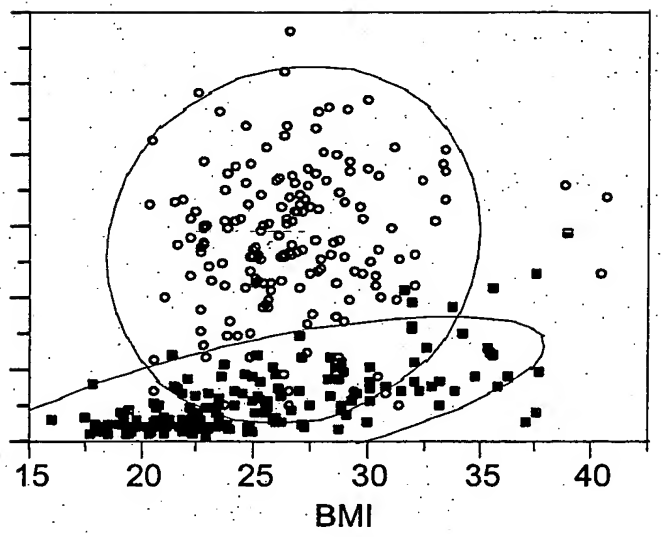
Patient TF: 39 year old gay male developed truncal adiposity, after 1 month of treatment he had a 1.5 inch reduction in waist size. Only adverse effect was slight foot swelling. He remains on rhGH therapy.

Patient HN: 27 year old hispanic gay male with advanced HIV disease (CD4 27) and previous treatment with all licensed PIs, developed truncal adiposity; after 2 months of therapy had slight improvement in truncal adiposity, lost 7 pounds. No associated side effects. He remains on rhGH therapy.

CONCLUSION:

RECOMBINANT HUMAN GROWTH HORMONE (*SEROSTIM™*) AT DOSES OF 5-6 MG/DAY IS EFFECTIVE IN REDUCING BUFFALO HUMPS AND TRUNCAL ADIPOSITY, BUT NOT PERIPHERAL LIPODYSTROPHY AND HYPERLIPIDEMIA ASSOCIATED WITH PI THERAPY. RELAPSE OF BUFFALO HUMP AND TRUNCAL ADIPOSITY OCCURS WITH DOSE REDUCTION OR DRUG DISCONTINUATION. ADVERSE AFFECTS INCLUDE INCREASE IN TISSUE TURGOR (FACIAL AND OR FOOT SWELLING, ARTHRALGIAS, CARPAL TUNNEL SYNDROME AND ONSET OR WORSENING OF DIABETES. SERIAL PHOTOS, BIA AND WAIST MEASUREMENTS ARE USEFUL IN FOLLOWING RESPONSE TO TREATMENT. OPTIMAL DOSE AND DURATION OF THERAPY ARE UNCLEAR AND DESERVE FURTHER INVESTIGATION.

Exhibit B



Plot of visceral adipose tissue (VAT) area at the level of L4-5 against Body Mass Index (BMI). Lines correspond to the 95% confidence bounds for a healthy male volunteer population (red squares) and a population of male individuals with HADDS (green circles). Note the lack of overlap of the two areas indicating marked differences in the relationship between BMI and visceral fat content in men with HADDS as compared to non-HIV infected men some of whom are obese (BMI>30).

STEDMAN'S Medical Dictionary

26th Edition

ILLUSTRATED IN **COLOR**

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A WAVERLY COMPANY

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95 96 97 98 99
2 3 4 5 6 7 8 9 10

Ω 1. Twenty-fourth and last letter of the Greek alphabet, omega. 2. Symbol for Ohm.

O 1. Symbol for oxygen; orotidine. 2. Abbreviation for opening (in formulas for electrical reactions). 3. Symbol for a blood group in the ABO system. See ABO blood group, Blood Groups appendix. 4. An abbreviation derived from *ohne Hauch* (without a film), used as a designation for: 1) antigens that occur in the bacterial cell, in contrast to those in the flagella; 2) specific antibodies for such somatic antigens; 3) the agglutinative reaction between somatic antigen and its antibody.

^{15}O. Symbol for oxygen-15.

^{16}O. Symbol for oxygen-16.

^{17}O. Symbol for oxygen-17.

^{18}O. Symbol for oxygen-18.

o- In chemistry, the abbreviation for ortho- (2).

oak ap·ple. SYN nutgall.

oari-, oario-. Obsolete term for an ovary. SEE oo-, oophor-, ovario-. [G. *ōarion*, a small egg, dim. of *ōon*, egg]

oath (ōth). A solemn affirmation or attestation. SEE Hippocratic Oath, Veterinarian's Oath.

OB Abbreviation for obstetrics.

ob·dor·mi·tion (ob-dōr-mish′ŭn). Numbness of an extremity, due to pressure on the sensory nerve. [L. *ob-dormio*, pp. *-itus*, to sleep]

O'Beirne, James, Irish surgeon, 1786–1862. SEE O'B.'s *sphincter.*

obe·li·ac (ō-bē′lē-ak). Relating to the obelion.

obe·li·ad (ō-bē′lē-ad). Toward the obelion.

obe·li·on (ō-bē′lē-on). A craniometric point on the sagittal suture between the parietal foramina near the lambdoid suture. [G. *obelos*, a spit]

Obermayer, Friedrich, Austrian physician, 1861–1925. SEE O.'s *test.*

Obermeier, Otto H.F., German physician, 1843–1873. SEE O.'s *spirillum.*

Obersteiner, H., Austrian neurologist, 1847–1922. SEE O.-Redlich *line*, *zone.*

obese (ō-bēs′). Excessively fat. SYN corpulent. [L. *obesus*, fat, partic. adj., fr. *ob-edo*, pp. *-esus*, to eat away, devour]

obe·si·ty (ō-bē′si-tē). An abnormal increase of fat in the subcutaneous connective tissues. SYN adiposity (1), corpulence, corpulency.

hypothalamic o., o. caused by disease of the hypothalamus.

hypothalamic o. with hypogonadism, SYN *dystrophia* adiposogenitalis.

morbid o., o. sufficient to prevent normal activity or physiologic function, or to cause the onset of a pathologic condition.

simple o., o. resulting when caloric intake exceeds energy expenditure.

obex (ō′beks) [NA]. The point on the midline of the dorsal surface of the medulla oblongata that marks the caudal angle of the rhomboid fossa or fourth ventricle. It corresponds to a small, transverse medullary fold overhanging the calamus scriptorius. [L. barrier]

ob·fus·ca·tion (ob-fus-kā′shŭn). 1. A rendering dark or obscure. 2. A deliberate attempt to confuse or to prevent understanding. [L. *ob-fusco*, pp. *-atus*, to darken, fr. *fuscus*, dark, tawny]

OB/GYN Abbreviation for obstetrics and gynecology.

ob·i·dox·ime chlo·ride (ob′ē-dok-sēm). A cholinesterase reactivator much like 2-PAM.

ob·ject (ob′jekt). 1. Anything to which thought or action is directed. 2. In psychoanalysis, that through which an instinct can achieve its aim. 3. In psychoanalysis, often used synonymously with person.

good o., in psychoanalysis, the good or supporting aspects of an important person in the patient's life, especially of a parent or parent-surrogate.

sex o., a person toward whom another is sexually attracted; a term usually used by a female to indicate that a male narrowly views her as a vehicle for sex while completely disregarding the rest of her persona.

test o., (1) an o. having very fine surface markings, mounted on a slide, used to determine the defining power of the objective lens of a microscope; (2) the target in measurement of the visual field.

ob·ject choice. In psychoanalysis, the object (usually a person) upon which psychic energy is centered.

ob·jec·tive (ob-jek′tiv). 1. The lens or lenses in the lower end of the body tube of a microscope, by means of which the rays coming from the object examined are brought to a focus. SYN object glass. 2. Viewing events or phenomena as they exist in the external world, impersonally, or in an unprejudiced way; open to observation by oneself and by others. Cf. subjective. [L. *ob-jicio*, pp. *-jectus*, to throw before]

achromatic o., an o. that is corrected for two colors chromatically, and one color spherically.

apochromatic o., an o. in which chromatic aberration is corrected for three colors and spherical aberration is corrected for two.

immersion o., a high power o. used with a drop of oil between the lens and the specimen on the slide, allowing a greater numerical aperture; similar lenses are available for use with water as the immersing liquid.

ob·jec·tive as·sess·ment da·ta. Those facts presented by the client that show his/her perception, understanding and interpretation of what is happening.

ob·li·gate (ob′li-gāt). Without an alternative system or pathway. [L. *ob-ligo*, pp. *-atus*, to bind to]

ob·lique (ob-lēk′). Slanting; deviating from the perpendicular, horizontal, sagittal, or coronal plane of the body. In radiography, a projection that is neither frontal nor lateral. [L. *obliquus*]

ob·liq·ui·ty (ob-lik′wi-tē). SYN asynclitism.

Litzmann o., inclination of the fetal head so that the biparietal diameter is oblique in relation to the plane of the pelvic brim, the posterior parietal bone presenting to the parturient canal. SYN posterior asynclitism.

Nägele o., inclination of the fetal head in cases of flat pelvis, so that the biparietal diameter is oblique in relation to the plane of the pelvic brim, the anterior parietal bone presenting to the parturient canal. SYN anterior asynclitism.

ob·li·qu·us (ob-lī′kwŭs). Denoting a structure having an oblique course or direction; a name given, with further qualification, to several muscles. SEE muscle. [L. slanting, oblique]

ob·lit·er·a·tion (ob-lit-er-ā′shŭn). Blotting out, especially by filling of a natural space or lumen by fibrosis or inflammation. In radiology, disappearance of the contour of an organ when the adjacent tissue has the same x-ray absorption. [L. *oblittero*, to blot out]

ob·lon·ga·ta (ob-long-gah′tă). SYN *medulla* oblongata. [L. fem. of *oblongatus*, from *oblongus*, rather long]

ob·nu·bi·la·tion (ab-nū′bil-ā′shun). A clouded mental state. [L. *ob-nubilo*, to becloud, obscure, fr. *nubes*, cloud]

OBS. SYN organic brain *syndrome.*

ob·ser·ver (ob-zer′ver). One who perceives, notices, or watches; in behavioral research with humans, the investigator or his/her surrogate. [L. *observo*, to watch]

nonparticipant o., an investigator who studies a group of subjects engaged in certain activities but does not directly participate in these activities, presumably being able to study them more objectively.

participant o., an investigator who while studying the activities of a group of subjects also participates in their activities, presumably being able to gain more detailed, relevant information but with less objectivity.

ob·ses·sion (ob-sesh′ŭn). A recurrent and persistent idea,

pan·cre·a·tin (li-pan'krē-ă-tin, -krē'ă-tin). SYN pancrelipase.

lip·a·ro·cele (lip'ă-rō-sēl). An omental hernia. [G. *liparos*, fatty, *kēlē*, tumor, hernia]

-pase (lip'ās). In general, any fat-splitting or lipolytic enzyme; a carboxylesterase; *e.g.*, triacylglycerol lipase, phospholipase A_2, lipoprotein lipase.

lip·ec·to·my (lip-ek'tō-mē). Surgical removal of fatty tissue, as in cases of adiposity. [lipo- + G. *ektomē*, excision]

le·de·ma (lip'e-dē'mă). Chronic swelling, usually of the lower extremities, particularly in middle-aged women, caused by the widespread even distribution of subcutaneous fat and fluid. [lipo- + G. *oidēma*, swelling]

li·pe·mia (lip-ē'mē-ă). The presence of an abnormally large amount of lipids in the circulating blood. SYN hyperlipidemia, hyperlipoidemia, lipidemia, lipoidemia. [lipid + G. *haima*, blood]

alimentary l., relatively transient l. occurring after the ingestion of foods with a large content of fat. SYN postprandial l.

diabetic l., development of lactescent plasma upon ingestion of dietary lipids; a rare manifestation of uncontrolled diabetes mellitus caused by defective metabolism of dietary lipids and abolished by the administration of insulin.

postprandial l., SYN alimentary l.

retina'lis, a creamy appearance of the retinal blood vessels that occurs when the lipids of the blood exceed 5%.

li·pe·mic (li-pē'mik). Relating to lipemia.

lipid. "Fat-soluble," an operational term describing a solubility characteristic, not a chemical substance, *i.e.*, denoting substances extracted from animal or vegetable cells by nonpolar or "fat" solvents; included in the heterogeneous collection of materials thus extractable are fatty acids, glycerides and glyceryl ethers, phospholipids, sphingolipids, alcohols and waxes, terpenes, steroids, and "fat-soluble" vitamins A, D, and E. [G. *lipos*, fat]

isotropic l., a l. in the form of doubly refractive droplets.

annular l., the layer(s) of l. bound to and/or surrounding an integral membrane protein.

brain l., impure cephalin possessing marked hemostatic action when locally applied.

compound l.'s, SYN heterolipids.

isotropic l., a l. occurring in the form of singly refractive droplets.

simple l.'s, SYN homolipids.

lip·i·de·mia (lip'i-dē'mē-ă). SYN lipemia.

lip·i·do·ly·tic (lip'i-dō-lit'ik). Causing breakdown of lipid. [lipid + G. *lysis*, loosening]

lip·i·do·sis, pl. **lip·i·do·ses** (lip-i-dō'sis, -sēz). Hereditary abnormality of lipid metabolism that results in abnormal amounts of lipid deposition; classification is typically based on the responsible enzymatic deficiency and type of lipid involved. Such enzymatic activity takes place in the lysosomes, and the abnormal products appear as lysosomal storage diseases. Sphingolipidoses make up the largest portion of recognized lipidoses, involving abnormal metabolism of gangliosides, ceramides, and cerebrosides. [lipid + G. *-ōsis*, condition]

ceramide lactoside l., an inherited disorder associated with an accumulation of ceramide lactoside due to a deficiency of ceramide lactosidase; results in progressive brain damage with liver and spleen enlargement.

cerebral l., SYN cerebral *sphingolipidosis*.

cerebroside l., SYN Gaucher's *disease*.

ganglioside l., SYN gangliosidosis.

glucolipid l., SYN Fabry's *disease*.

sphingomyelin l., SYN Niemann-Pick *disease*.

sulfatide l., SYN metachromatic *leukodystrophy*.

Lipmann, Fritz A., German-U.S. biochemist in the U.S. and Nobel laureate, 1899–1986. SEE Warburg-L.-Dickens-Horecker reagent

lipo-. Fatty, lipid. [G. *lipos*, fat]

lip·am·ide (lip-ō-am'īd, -am'id). SEE lipoic acid.

lip·am·ide de·hy·dro·gen·ase. SYN dihydrolipoamide dehydrogenase.

lip·o·am·ide di·sul·fide. Oxidized lipoic acid in amide combination with the ε-amino group of an L-lysyl residue of pyruvic acid dehydrogenase..

lip·o·am·ide re·duc·tase (NADH). SYN dihydrolipoamide dehydrogenase.

lip·o·ar·thri·tis (lip'ō-ar-thrī'tis). Inflammation of the periarticular fatty tissues of the knee. [lipo- + arthritis]

lip·o·ate (lip'ō-āt). A salt or ester of lipoic acid.

lip·o·ate ace·tyl·trans·fer·ase. SYN dihydrolipoamide acetyltransferase.

lip·o·a·tro·phia (lip'ō-ă-trō'fē-ă). SYN lipoatrophy.

l. annula'ris, a rare condition of unknown cause characterized by localized panatrophy, a depressed area encircling the arm with sclerosis and atrophy of fat.

l. circumscrip'ta, localized fat atrophy.

lip·o·at·ro·phy (lip-ō-at'rō-fē). Loss of subcutaneous fat, which may be total, congenital, and associated with hepatomegaly, excessive bone growth, and insulin-resistant diabetes. SYN Lawrence-Seip syndrome, lipoatrophia, lipoatrophic diabetes. [G. *lipos*, fat, + *a-*, priv. + *trophē*, nourishment]

insulin l., SYN insulin *lipodystrophy*.

partial l., SYN progressive *lipodystrophy*.

lip·o·blast (lip'ō-blast). An embryonic fat cell. [lipo- + G. *blastos*, germ]

lip·o·blas·to·ma (lip'ō-blas-tō'mă). **1.** SYN liposarcoma. **2.** A benign subcutaneous tumor composed of embryonal fat cells separated into distinct lobules, occurring usually in infants.

lip·o·blas·to·ma·to·sis (lip'ō-blas-tō-mă-tō'sis). A diffuse form of lipoblastoma that infiltrates locally but does not metastasize.

lip·o·car·di·ac (lip'ō-kar'dē-ak). **1.** Relating to fatty heart. **2.** Denoting a person suffering from fatty degeneration of the heart. [lipo- + G. *kardia*, heart]

lip·o·cat·a·bol·ic (lip'ō-kat-ă-bol'ik). Relating to the breakdown (catabolism) of fat.

lip·o·cer·a·tous (lip-ō-ser'ă-tŭs). SYN adipoceratous.

lip·o·cere (lip'ō-sēr). SYN adipocere. [lipo- + L. *cera*, wax]

lip·o·chon·dria (lip'ō-kon'drē-ă). Temporary storage vacuoles of lipids found in the Golgi apparatus. SEE ALSO phytosterolemia. [lipo- + mitochondria]

lip·o·chon·dro·dys·tro·phy (lip'ō-kon-drō-dis'trō-fē). SYN Hurler's *syndrome*.

lip·o·chrome (lip'ō-krōm). **1.** A pigmented lipid, *e.g.*, lutein, carotene. SYN chromolipid. **2.** A term sometimes used to designate the wear-and-tear pigments, *e.g.*, lipofuscin, hemofuscin, ceroid. More precisely, l.'s are yellow pigments that seem to be identical to carotene and xanthophyll and are frequently found in the serum, skin, adrenal cortex, corpus luteum, and arteriosclerotic plaques, as well as in the liver, spleen, and adipose tissue; l.'s do not stain with the ordinary dyes for fat. **3.** The pigment produced by certain bacteria. [lipo- + G. *chroma*, color]

li·poc·la·sis (li-pok'lă-sis). SYN lipolysis. [lipo- + G. *klasis*, a breaking]

lip·o·clas·tic (lip-ō-klas'tik). SYN lipolytic.

lip·o·crit (lip'ō-krit). An apparatus and procedure for separating and volumetrically analyzing the amount of lipid in blood or other body fluid. [lipo- + G. *krinō*, to separate]

lip·o·cyte (lip'ō-sīt). SYN fat-storing *cell*. [lipo- + G. *kytos*, cell]

lip·o·der·moid (lip-ō-der'moyd). Congenital, yellowish-white, fatty, benign tumor located subconjunctivally. [lipo- + dermoid]

lip·o·di·er·e·sis (lip'ō-dī-er'ĕ-sis). SYN lipolysis. [lipo- + G. *dieresis*, division]

lip·o·dys·tro·phia (lip'ō-dis-trō'fē-ă). SYN lipodystrophy.

l. intestina'lis, obsolete term for Whipple's *disease*.

l. progressi'va supe'rior, SYN progressive *lipodystrophy*.

lip·o·dys·tro·phy (lip-ō-dis'trō-fē) [MIM*157660]. Defective metabolism of fat. SYN lipodystrophia. [lipo- + G. *dys-*, bad, difficult, + *trophē*, nourishment]

congenital total l. [MIM*151680, MIM*151670, MIM*308908], l. characterized by almost complete lack of subcutaneous fat, accelerated rate of growth and skeletal development